REMARKS

The examiner has rejected claims 9-11 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements. Applicant has amended claim 9 to require the presence of an additional element.

The examiner has rejected claims 1-6 and 9-12 as obvious over the combination of Cooke et al. (U.S. Patent 4,725,549) and A.M. Walker (*TEM*, 5(5): 195-200, 1994) in view of Maciejewski et al. (*J. Biol. Chem.*, 270(17): 27661-27665, 1995).

The examiner acknowledges that Cooke et al. do not teach a nucleic acid encoding a prolactin with a substitution at the serine corresponding to position 179 of human prolactin. The examiner further acknowledges that the Walker reference does not teach prolactin with a substitution at serine within the region of amino acids 170-180. The examiner contends that it would have been obvious to modify the Cooke et al. teaching (of a recombinant production of prolactin) in the manner taught by Maciejewski et al. (in order to create a prolactin receptor antagonist).

Applicant respectfully and vigorously disagrees that either Cooke et al. or the 1994 Walker reference or some hypothetical combination of the two would meaningfully be modified "in the manner taught by Maciejewski et al." in order to create a prolactin receptor antagonist.

First, the 1994 Walker reference and Maciejewski et al. teach away from each other. Thus, Applicant has noted in her application that serine 90 phosphorylated bovine prolactin was reported to be biologically inactive (see page 2, lines 15-18). But as acknowledged by the examiner, Maciejewski et al. teach the mutation of serine at amino acid position 90 of bovine prolactin. The lack of biological activity for the prolactin substituted by Maciejewski et al. is in stark contrast to the

present invention in which Applicant's differently substituted prolactin acts as an antagonist to non-phosphorylated prolactin, and inhibits cell proliferation of Nb2 cells (see page 2, lines 25-31; page 5, lines 5-7; page 6, lines 12-14). Further, the 1994 Walker references teaches monophosphorylated PRL is an antagonist to nonphosphorylated PRL (see page 197, column 3), while Maciejewski et al. state that "[p]hosphorylated rat or bovine PRL is not active in the Nb2 rat lymphoma bioassay, whereas the nonphosphorylated form is mitogenic" (see page 27661, column 2). Thus, in fact, Maciejewski et al. suggest that phosphorylated PRL is not an antagonist to non-phosphorylated PRL.

> Phosphorylated bPRL does not compete with ^{125}I-labeled nonphosphorylated bPRL for binding to the intermediate form of the PRL receptor found in NB2 cells. The failure of phosphorylated bPRL to bind to the PRL receptor suggests that phosphorylation removed the binding determinants of site 1 from the spatial relationship required for receptor binding; in other words, phosphorylation has induced a conformation change.

See page 27661, column 2. Since phosphorylated bPRL does not bind to the PRL receptor, it is not an antagonist to nonphosphorylated bPRL. Therefore, the examiner's suggested combination whereby the Cooke et al. and Walker 1994 references would be modified "in the manner taught by Maciejewski et al." is not a proper combination of references and does not suggest or make obvious the subject invention as described and claimed.

Further, the examiner has not provided any motivation or suggestion to combine the prior art references. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01 at 2100-98, *citing In re Fine*, 837 F.2d 1071, t USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The

mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01 at 2100-98, *citing In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Rather, the examiner impermissibly uses the teachings of Applicant in her subject application in an attempt to provide motivation to combine the references. "It is difficult but necessary that the decisionmaker forget what he or she has been taught ... about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." MPEP 2141.01 at 2100-91, *quoting W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The examiner states that Maciejewski et al. teach the mutation of serine 90 of bovine prolactin with glutamic acid and that the substitution mimics phosphorylation of the prolactin, such that the substituted prolactin acts as a prolactin receptor antagonist. However, Maciejewski et al. only measured the biological activity of the mutation of serine 90 of bovine prolactin with glutamic acid. The article does not state that the substituted prolactin acts as a prolactin receptor antagonist. In fact, Maciejewski et al. suggest that phosphorylated PRLs could not be used as antagonists. "Phosphorylated PRLs appear to have altered structure, because they have unique biological activities or are unable to bind or activate PRL receptors to initiate biological actions" (see page 27661, column 2). The examiner also contends that the Maciejewski et al. reference teaches a substitution that mimics phosphorylation of the prolactin, such that the substituted prolactin acts as a prolactin receptor agonist, and refers to page 27664, Fig. 5. The examiner has misinterpreted since the figure

is not an assay such as to demonstrate antagonism. Rather in Fig. 5 Maciejewski et al. only indicates the biological activity of each of the prolactins alone, and further notes that the biological activity of S90E BPRL was dramatically reduced.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP 2141.02 at 2100-95, *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP 2143.01 at 2100-99, *citing In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Maciejewski et al. provide no suggestion or motivation to make the proposed modification because mutating prolactin would render it biologically inactive.

Thus, one skilled in the art would not modify the recombinant prolactin of Cooke et al. by the substitution of another amino acid for serine "in the manner" taught by Maciejewski et al. in order to create a prolactin receptor antagonist because Maciejewski et al. do not teach the use of phosphorylated PRLs as antagonists!

In addition, the examiner states that one would be motivated in substituting another amino acid, such as glutamic acid as was taught by Maciejewski et al., because this would create a prolactin which would mimic phosphorylated prolactin (without the disadvantage of possible dephosphorylation). However, the disadvantage of possible dephosphorylation is not discussed in any of the references, but rather in the application itself (page 3, lines 7-10). "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." MPEP 2142, 2143 at 2100-97, *citing In re*

Vaeck, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991). The examiner's statement is therefore impermissible hindsight.

In conclusion, the subject claims are novel and unobvious over the cited art. Nevertheless, Applicant includes with this response her declaration setting out animal trials in which some initial results are given for use of the prolactin mutant described and claimed in the subject application. As seen in this declaration, the inventively mutated prolactin yielded quite promising results. There is currently no good therapy available for the later stages of prostate cancer. Thus these early, promising results for the inventively mutated prolactin are surprisingly effective, and further demonstrate the novel and unobvious nature of the invention.

Accordingly, Applicant believes that pending claims 1-6, 9-11, and 14-16 define novel and unobvious subject matter, and an early indication of allowability is respectfully requested.

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Respectfully submitted,

J. Suzanne Siebert, Reg. No. 28,758
MAJESTIC, PARSONS, SIEBERT & HSUE P.C.
Four Embarcadero Center, Suite 1100
San Francisco, California 94111-4106
Telephone: (415) 248-5500
Facsimile: (415) 362-5418